UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/441,857	11/18/1999	HAO-PENG XU DUFFY	52494/2202	5116

26646 7590 09/11/2003

KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	20

DATE MAILED: 09/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/441,857	DUFFY ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,7-12 and 70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,7-12 and 70* is/are rejected.

7)☐ Claim(s) *2,3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim 70 has been amended. Claims 1-3, 7-12 and 70 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The objection to claims 2 and 3, and claims 7-12 in part, for being dependent upon a rejected base claim, is maintained for reasons of record.

The rejection of claims 1, 7-12 and 70 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 is drawn to an isolated nucleic acid comprising a sequence encoding a wth3 protein. Claim 70 embodies the nucleic acid of claim 1 operatively linked to a regulatory sequence. Claims 7-12 are drawn in part to the nucleic acid of claim 1. The specification states on page 3, lines 15-18 that the isolate nucleic acids of the invention "can" encode an amino acid sequence comprising SEQ ID NO:12 from about amino acid residue number 1 to amino acid residue number 175 and that the nucleic acid sequence "can" be SEQ ID NO:7 or SEQ ID NO:11. Given the broadest reasonable interpretation, the nucleic acids of the invention are not confined to those encoding SEQ ID NO:12 and can include allelic variants, splice variants and nucleic acids encoding homologs and variant proteins differing in structure and function from SEQ ID NO:12.

The specification describes the nucleic acid sequences of SEQ ID NO:7 and 11 and the amino acid sequence of SEQ ID NO:12. The specification does not describe allelic variants or splice variants. The general knowledge of the art concerning allelic, polymorphic or splice variants does not provide any indication of how the structure of the polynucleotides encoding SEQ ID NO:12 are representative of the undisclosed allelic, polymorphic or splice variant

sequences. The common attributes of this genus has not been described. With the exception of the nucleic acids encoding SEQ ID NO:12, one of skill in the art would conclude that the applicant was not in possession of the claimed genus because the species encoding SEQ ID NO:12 are not representative of all the variants of the genus and therefore insufficient to support the claim.

Further, the claims are broadly drawn to encompass nucleic acid encoding wth3 proteins beyond those limited to SEQ ID NO:12. The specification and claim 1 do not indicate what distinguishing attributes are shared by members of the genus of wth3 proteins. Thus, the specification does not place any limits on the number of amino acid substitutions, deletions, insertions or additions that may be made to SEQ ID NO:12 with the scope of a wth3 protein. Thus the scope of claim 1 is highly varied because a significant number of both structural and functional differences between members of the claimed genus is encompassed by the claim. Since the claim fails to limit the common attributes of the claimed genus in terms of both structure and function, and because the genus is highly variant, the polynucleotides encoding SEQ ID NO:12 are insufficient to describe the genus of polynucleotides encoding a wth3 protein. One of skill in the art would reasonably conclude that the specification fails to provide a representative number of species to describe the genus, and thus, the applicant was not in possession of the claimed genus at the time of filing.

Applicant argues that the genus of wth3 proteins is well described by the specification specifically citing the location of the WTH3 protein in chromosome 2q31, the length of the mRNA transcript , the coding sequence and its homology to a family of proteins of known genetic function, and the downregulation of WTH3 in cells exhibiting multiple drug resistance and the differential methylation of WTH3. this has been considered but not found persuasive. The passages in the specification referred to in applicants argument do not represent a limiting definition for the genus of wth3 proteins, and exemplify only the instant disclosed WTH3 gene and protein translated therefrom. Even if the characteristics described by applicant were used as claim limitations, the claims would still read on a genus of proteins encompassing neutral allelic variants and homologs. The nature of both neutral allelic variants and homologs is that they are variant structures, and the structure of one does not serve to indicate the structure of other

unknown allelic variants or homologs. The art teaches that an allele is an alternate form of a gene occupying the same locus in a particular chromosome and differing from other alleles at one or more mutational sites. The Glossary of Genetics (Reiger et al, 1991, pages 16-17) discloses that there are at least seven different kinds of allele in addition to the "strictly neutral" type. The alleles are distinguished by the effects that the different structural variant ions have on phenotype, and thus different allelic proteins may function differently as a result of the alterations in amino acid sequence. There is no description in the specification of how the structure of SEQ ID NO:11 related to the structure of other unknown alleles. With regard to homologs, it is known in the art that more often than not, a protein which is identified as a homolog in another species does not have the functional characteristics expected of said homolog based on the sequence homology between the two proteins . Bork and Koonin (Nature Genetics, 1998, Vol. 18, pp. 313-318) state that "more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from the homologue to the query (page 315, second column, lines 11-16, under the heading "Effects of noise on functional predictions"). Even in the event that the claims were amended to recite the limitations argued by the applicant, one of skill in the art would reasonable conclude that applicant did not disclose a representative number of species which would characterize the genus. Therefore, applicant was not in possession of the claimed genus.

Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated vectors and isolated host cells comprising said vectors, does not reasonably provide enablement for vectors and host cells comprised within a transgenic animal or an animal or human being having been treated by gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The specification states on page 22 lines 30-31 that "nucleic acids which are homologous to wth3 can be useful for treatment of cells and tumors exhibiting multiple drug resistance". Thus, the specification contemplates the use of the instant polynucleotides in gene therapy for the treatment of tumors exhibiting multiple drug resistance. Thus, when given the broadest

reasonable interpretation claims drawn to host cells and expression vectors encompass host cells and expression vectors within patient having received gene therapy or within a transgenic animal. The specification is not enabling for these uses for the following reasons:

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen

presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that in 1995 current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 7-9 and 70 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. For the reasons stated in the rejection under 112, first paragraph above, the claims can be construed as reading on a expression vector or a host cell comprised within a patient who has undergone a gene therapy procedure. Amendment of the claims to recite "isolated expression vector" and "isolated host cell" would overcome this rejection..

All other rejections and objections as set forth in Paper no. 17 are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
8/11/03